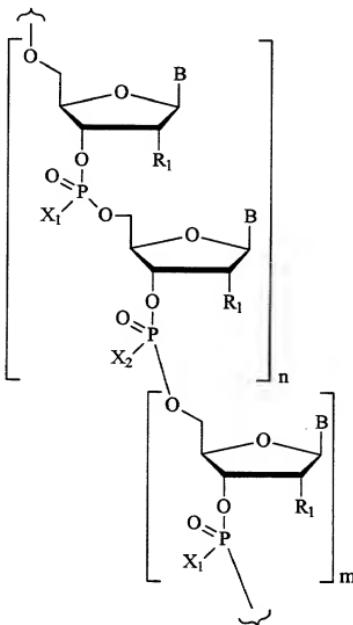


## WHAT IS CLAIMED IS:

1. A compound comprising a plurality of covalently-bound 2'-modified nucleosides having the formula:



5 wherein:

each B is a nucleobase;

one of X<sub>1</sub> or X<sub>2</sub> is O, and the other of X<sub>1</sub> or X<sub>2</sub> is S;

each R<sub>1</sub> is, independently, H, hydroxyl, C<sub>1</sub>-C<sub>20</sub> alkyl, C<sub>3</sub>-C<sub>20</sub> alkenyl, C<sub>2</sub>-C<sub>20</sub> alkynyl, halogen, thiol, keto, carboxyl, 10 nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-

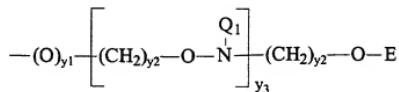
phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, or polyether;

or  $R_1$  is a group of formula  $Z-R_{22}-(R_{23})_v$ ;  
 $Z$  is O, S, NH, or  $N-R_{22}-(R_{23})_v$ ;  
 $R_{22}$  is  $C_1-C_{20}$  alkyl,  $C_2-C_{20}$  alkenyl, or  $C_2-C_{20}$  alkynyl;

$R_{23}$  is hydrogen, amino, halogen, hydroxyl, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, polyether, a group that enhances the pharmacodynamic properties of oligonucleotides, or a group that enhances the pharmacokinetic properties of oligonucleotides;

$v$  is from 0 to about 10;

or  $R_1$  has the formula:

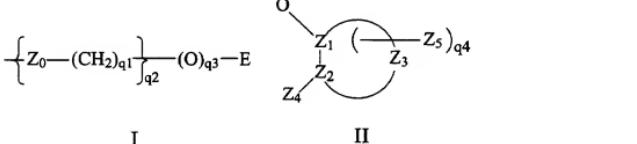


$y_1$  is 0 or 1;  
 $y_2$  is independently 0 to 10;  
 $y_3$  is 1 to 10;  
 $E$  is  $C_1-C_{10}$  alkyl,  $N(Q_1)(Q_2)$  or  $N=C(Q_1)(Q_2)$ ;

each  $Q_1$  and  $Q_2$  is, independently, H,  $C_1$ - $C_{10}$  alkyl, substituted alkyl, dialkylaminoalkyl, a nitrogen protecting group, a tethered or untethered conjugate group, a linker to a solid support; or  $Q_1$  and  $Q_2$ , together, are 5 joined in a nitrogen protecting group or a ring structure that can include at least one additional heteroatom selected from N and O;

or  $R_1$  has one of formula I or II:

10



wherein

$Z_0$  is O, S, or NH;  
 $q^1$  is from 0 to 10;  
15  $q^2$  is from 1 to 10;  
 $q^3$  is 0 or 1;  
 $q^4$  is, 0, 1 or 2;  
 $Z_4$  is  $\text{OM}_1$ ,  $\text{SM}_1$ , or  $\text{N}(\text{M}_1)_2$ ;  
each  $\text{M}_1$  is, independently, H,  $C_1$ - $C_8$  alkyl,  $C_1$ - $C_8$  20 haloalkyl,  $\text{C}(\text{=NH})\text{N}(\text{H})\text{M}_2$ ,  $\text{C}(\text{=O})\text{N}(\text{H})\text{M}_2$  or  $\text{OC}(\text{=O})\text{N}(\text{H})\text{M}_2$ ;  
 $\text{M}_2$  is H or  $C_1$ - $C_8$  alkyl;  
 $Z_1$ ,  $Z_2$  and  $Z_3$  comprise a ring system having from about 4 to about 7 carbon atoms, or having from about 3 to about 6 carbon atoms and 1 or 2 hetero atoms wherein said 25 hetero atoms are selected from oxygen, nitrogen and sulfur, and wherein said ring system is aliphatic, unsaturated aliphatic, aromatic, or saturated or unsaturated heterocyclic; and

$Z_5$  is alkyl or haloalkyl having 1 to about 10 carbon atoms, alkenyl having 2 to about 10 carbon atoms, alkynyl having 2 to about 10 carbon atoms, aryl having 6 to about 14 carbon atoms,  $N(Q_1)(Q_2)$ ,  $OQ_1$ , halo,  $SQ_1$  or  $CN$ ;

5         $n$  is from 2 to 50; and

$m$  is 0 or 1.

2.        The compound of claim 1 wherein  $R_1$  is  $-O-CH_2-CH_2-O-$   
 $CH_3$ .

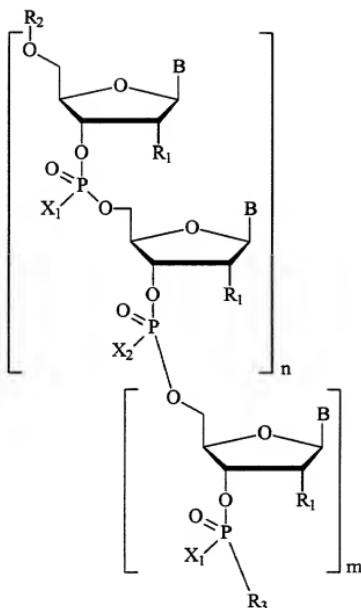
3.        The compound of claim 1 wherein  $n$  is about 5 to  
10 about 50.

4.        The compound of claim 1 wherein  $n$  is about 8 to  
about 30.

5.        The compound of claim 1 wherein  $n$  is about 4 to  
about 15.

15        6.        The compound of claim 1 wherein  $n$  is 2 to about  
10.

7.        An oligonucleotide having the Formula:



wherein:

each B is a nucleobase;

X<sub>1</sub> is S;

5        X<sub>2</sub> is O;

each R<sub>1</sub> is, independently, H, hydroxyl, C<sub>1</sub>-C<sub>20</sub> alkyl, C<sub>3</sub>-C<sub>20</sub> alkenyl, C<sub>2</sub>-C<sub>20</sub> alkynyl, halogen, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-10 aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter

molecule, conjugate, polyamine, polyamide, polyalkylene glycol, or polyether;

or  $R_1$  is a group of formula  $Z-R_{22}-(R_{23})_v$ ;

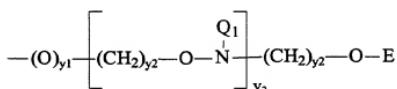
$Z$  is O, S, NH, or  $N-R_{22}-(R_{23})_v$ ;

5  $R_{22}$  is  $C_1-C_{20}$  alkyl,  $C_2-C_{20}$  alkenyl, or  $C_2-C_{20}$  alkynyl;

$R_{23}$  is hydrogen, amino, halogen, hydroxyl, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-10 dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, 15 polyalkylene glycol, polyether, a group that enhances the pharmacodynamic properties of oligonucleotides, or a group that enhances the pharmacokinetic properties of oligonucleotides;

$v$  is from 0 to about 10;

20 or  $R_1$  has the formula:



$y_1$  is 0 or 1;

$y_2$  is independently 0 to 10;

$y_3$  is 1 to 10;

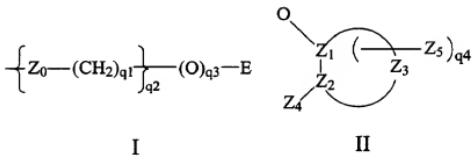
25  $E$  is  $C_1-C_{10}$  alkyl,  $N(Q_1)(Q_2)$  or  $N=C(Q_1)(Q_2)$ ;

each  $Q_1$  and  $Q_2$  is, independently, H,  $C_1-C_{10}$  alkyl, substituted alkyl, dialkylaminoalkyl, a nitrogen protecting group, a tethered or untethered conjugate group,

a linker to a solid support; or  $Q_1$  and  $Q_2$ , together, are joined in a nitrogen protecting group or a ring structure that can include at least one additional heteroatom selected from N and O;

5

or  $R_1$  has one of formula I or II:



wherein

10  $Z_0$  is O, S, or NH;  
 $q^1$  is from 0 to 10;  
 $q^2$  is from 1 to 10;  
 $q^3$  is 0 or 1;  
 $q^4$  is, 0, 1 or 2;

15  $Z_4$  is  $\text{OM}_1$ ,  $\text{SM}_1$ , or  $\text{N}(\text{M}_1)_2$ ;  
each  $\text{M}_1$  is, independently, H,  $\text{C}_1\text{-C}_8$  alkyl,  $\text{C}_1\text{-C}_8$  haloalkyl,  $\text{C}(\text{=NH})\text{N}(\text{H})\text{M}_2$ ,  $\text{C}(\text{=O})\text{N}(\text{H})\text{M}_2$  or  $\text{OC}(\text{=O})\text{N}(\text{H})\text{M}_2$ ;  
 $\text{M}_2$  is H or  $\text{C}_1\text{-C}_8$  alkyl;  
 $Z_1$ ,  $Z_2$  and  $Z_3$  comprise a ring system having from  
20 about 4 to about 7 carbon atoms, or having from about 3 to  
about 6 carbon atoms and 1 or 2 hetero atoms wherein said  
hetero atoms are selected from oxygen, nitrogen and sulfur,  
and wherein said ring system is aliphatic, unsaturated  
aliphatic, aromatic, or saturated or unsaturated  
25 heterocyclic; and

$Z_5$  is alkyl or haloalkyl having 1 to about 10  
carbon atoms, alkenyl having 2 to about 10 carbon atoms,

alkynyl having 2 to about 10 carbon atoms, aryl having 6 to about 14 carbon atoms,  $N(Q_1)(Q_2)$ ,  $OQ_1$ , halo,  $SQ_1$  or  $CN$ ;

n is from 2 to 50; and

m is 0 or 1;

5 R<sub>2</sub> is H, a hydroxyl protecting group, or an oligonucleotide; and

R<sub>3</sub> is OH, an oligonucleotide, or a linker connected to a solid support.

8. The compound of claim 7 wherein R<sub>1</sub> is -O-CH<sub>2</sub>-CH<sub>2</sub>-O-  
10 CH<sub>3</sub>.

9. The compound of claim 8 wherein R<sub>2</sub> is H, and R<sub>3</sub> is OH.

10. The compound of claim 8 wherein R<sub>2</sub> is a phosphodiester-linked oligonucleotide or a phosphorothioate linked oligonucleotide.

11. The compound of claim 8 R<sub>3</sub> is a phosphodiester-linked oligonucleotide or a phosphorothioate linked oligonucleotide.

12. R<sub>2</sub> and R<sub>3</sub> are each a phosphodiester-linked  
20 oligonucleotide or a phosphorothioate linked oligonucleotide.

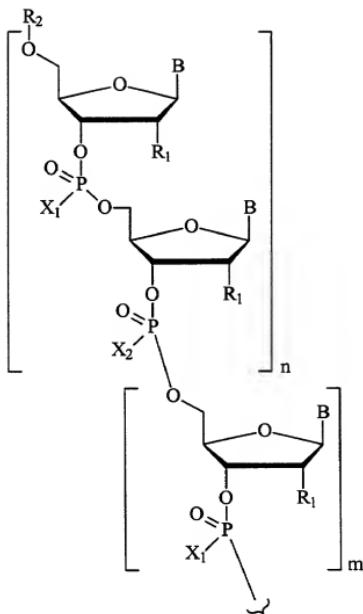
13. A compound having the Formula:

(5') W<sup>1</sup>-W<sup>2</sup>-W<sup>3</sup> (3')

wherein:

25 W<sup>1</sup> has the Formula:

100-200-1000-1000



wherein:

each B is a nucleobase;

one of  $X_1$  or  $X_2$  is O, and the other of  $X_1$  or  $X_2$  is S;

5 each  $R_1$  is, independently, H, hydroxyl,  $C_1-C_{20}$  alkyl,  $C_3-C_{20}$  alkenyl,  $C_2-C_{20}$  alkynyl, halogen, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-

phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene 5 glycol, or polyether;

or  $R_1$  is a group of formula  $Z-R_{22}-(R_{23})_v$ ;

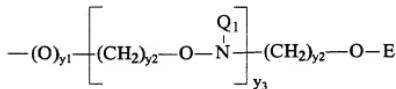
$Z$  is O, S, NH, or  $N-R_{22}-(R_{23})_v$ ;

$R_{22}$  is  $C_1-C_{20}$  alkyl,  $C_2-C_{20}$  alkenyl, or  $C_2-C_{20}$  alkynyl;

$R_{23}$  is hydrogen, amino, halogen, hydroxyl, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, 10 hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, polyether, a group that enhances the pharmacodynamic properties of oligonucleotides, or a group 15 that enhances the pharmacokinetic properties of oligonucleotides;

$v$  is from 0 to about 10;

or  $R_1$  has the formula:



25  $y_1$  is 0 or 1;

$y_2$  is independently 0 to 10;

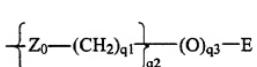
$y_3$  is 1 to 10;

$E$  is  $C_1-C_{10}$  alkyl,  $N(Q_1)(Q_2)$  or  $N=C(Q_1)(Q_2)$ ;

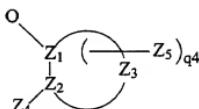
each  $Q_1$  and  $Q_2$  is, independently, H,  $C_1-C_{10}$  alkyl, substituted alkyl, dialkylaminoalkyl, a nitrogen protecting group, a tethered or untethered conjugate group, a linker to a solid support; or  $Q_1$  and  $Q_2$ , together, are 5 joined in a nitrogen protecting group or a ring structure that can include at least one additional heteroatom selected from N and O;

or  $R_1$  has one of formula I or II:

10



I



II

wherein

$Z_0$  is O, S, or NH;  
 $q^1$  is from 0 to 10;  
15  $q^2$  is from 1 to 10;  
 $q^3$  is 0 or 1;  
 $q^4$  is, 0, 1 or 2;  
 $Z_4$  is  $OM_1$ ,  $SM_1$ , or  $N(M_1)_2$ ;  
each  $M_1$  is, independently, H,  $C_1-C_8$  alkyl,  $C_1-C_8$  20 haloalkyl,  $C(=NH)N(H)M_2$ ,  $C(=O)N(H)M_2$  or  $OC(=O)N(H)M_2$ ;  
 $M_2$  is H or  $C_1-C_8$  alkyl;

$Z_1$ ,  $Z_2$  and  $Z_3$  comprise a ring system having from about 4 to about 7 carbon atoms, or having from about 3 to about 6 carbon atoms and 1 or 2 hetero atoms wherein said 25 hetero atoms are selected from oxygen, nitrogen and sulfur, and wherein said ring system is aliphatic, unsaturated aliphatic, aromatic, or saturated or unsaturated heterocyclic; and

$Z_5$  is alkyl or haloalkyl having 1 to about 10 carbon atoms, alkenyl having 2 to about 10 carbon atoms, alkynyl having 2 to about 10 carbon atoms, aryl having 6 to about 14 carbon atoms,  $N(Q_1)(Q_2)$ ,  $OQ_1$ , halo,  $SQ_1$  or  $CN$ ;

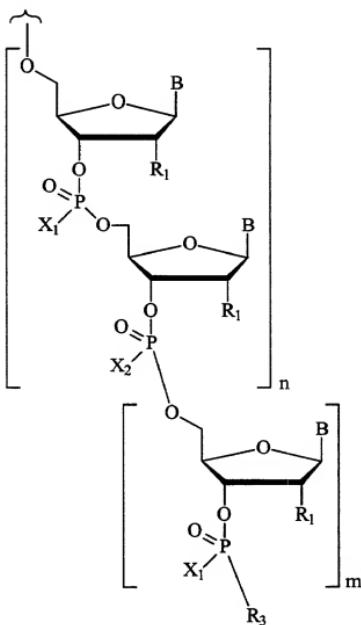
5         $n$  is from 2 to 50; and

$m$  is 0 or 1;

$R_2$  is H, a hydroxyl protecting group, or an oligonucleotide;

$W^3$  has the Formula:

10



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wherein  $R_3$  is OH, an oligonucleotide, or a linker connected to a solid support; and

$W^2$  is a plurality of covalently bound nucleosides linked by phosphodiester or phosphorothioate linkages.

5 14. The compound of claim 13 wherein  $R_1$  is  $-O-CH_2-CH_2-O-$   
 $CH_3$ .

15. The compound of claim 14 wherein  $R_2$  is H, and  $R_3$  is OH.

10 16. The compound of claim 14 wherein n is about 5 to about 50.

17. The compound of claim 14 wherein n is about 8 to about 30.

15 18. The compound of claim 14 wherein n is about 4 to about 15.

19. The compound of claim 14 wherein n is 2 to about 10.

20. The compound of claim 14 wherein  $W^2$  is a plurality of covalently bound nucleosides linked by phosphodiester linkages.

21. The compound of claim 14 wherein  $W^2$  is a plurality of covalently bound nucleosides linked by phosphorothioate linkages.

25 22. A composition comprising a compound of claim 1 and an acceptable carrier.

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23. A composition comprising a compound of claim 7 and an acceptable carrier.

24. A composition comprising a compound of claim 12 and an acceptable carrier.

5 25. A method of modulating the production or activity of a protein in an organism, comprising contacting said organism with a compound of claim 1.

10 26. A method of modulating the production or activity of a protein in an organism, comprising contacting said organism with a compound of claim 7.

27. A method of modulating the production or activity of a protein in an organism, comprising contacting said organism with a compound of claim 13.

15 28. A method of treating an organism having a disease characterized by the undesired production of a protein, contacting said organism with a compound of claim 1.

20 29. A method of treating an organism having a disease characterized by the undesired production of a protein, contacting said organism with a compound of claim 7.

30. A method of treating an organism having a disease characterized by the undesired production of a protein, contacting said organism with a compound of claim 13.

31. A method of assaying a nucleic acid, comprising 25 contacting a solution suspected to contain said nucleic acid with a compound of claim 1.

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32. A method of assaying a nucleic acid, comprising  
contacting a solution suspected to contain said nucleic acid  
with a compound of claim 7.

33. A method of assaying a nucleic acid, comprising  
5 contacting a solution suspected to contain said nucleic acid  
with a compound of claim 13.

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